CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: February 8, 2000	**DUE DATE:** July 20, 2000	**OPDRA CONSULT #:** 00-0046

TO: John Jenkins, M.D.
Acting Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH: Steve McCort, Project Manager
HFD-510

PRODUCT NAME: Unithroid (levothyroxine sodium tablets, USP; 0.025, 0.05, 0.075, 0.088, 0.1, 0.112, 0.125, 0.15, 0.175, 0.2, and 0.3 mg) **NDA #:** 21-210	**MANUFACTURER**: Jerome Stevens Pharmaceuticals, Inc. Bohemia, NY 11716

SAFETY EVALUATOR: Carol Pamer, R.Ph.

SUMMARY: In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), OPDRA conducted a review of the proposed proprietary name "Unithroid" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: From a safety perspective, OPDRA does not object to the use of the name "Unithroid". See the checked box below. We also reviewed the AERS postmarketing safety reports of medication errors associated with levothyroxine products and offer suggestions for prevention of further errors.

☐ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☒ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from this date forward.

☐ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDAs from this date forward.

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Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: **June 22, 2000**

NDA NUMBER: **21-210**

NAME OF DRUG: **Unithroid (levothyroxine sodium tablets, USP; (0.025, 0.05, 0.075, 0.088, 0.1, 0.112, 0.125, 0.15, 0.175, 0.2, 0.3 mg)**

NDA HOLDER: **Jerome Stevens Pharmaceuticals, Inc. Bohemia, NY 11716**

I. INTRODUCTION

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510) for assessment of the tradename Unithroid. Note, however, that in the late stages of finalization of this review (June 19, 2000), the sponsor withdrew the name "Unithroid" and proposed an alternate trade name [ ] for this product. The subject of this consult, however, is **only** a review of the proposed trade name "Unithroid". A separate analysis and consult will be provided to HFD-510 for the name [ ]".

Unithroid is an oral tablet product containing levothyroxine sodium. Historically, levothyroxine sodium products have been marketed in the U.S. without NDAs. This NDA was submitted in response to a Federal Register Notice published August 14, 1997, which requires that the manufacturers of all levothyroxine-containing drug products submit an NDA to market these products. Unithroid will be available in 11 oral tablet strengths: 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.2 mg, and 0.3 mg.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound alike or look alike to Unithroid to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's (USPTO) Text and Image Database was also conducted[v]. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three (3) prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

A group discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name Unithroid. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

A number of proprietary names were identified which contained the phrase "Uni" or a related phrase: ***Univasc, Unasyn, Unidur, Uniphyl, and Unituss***. The dosage forms and usual dosing of these products appear in Table 1.

Of these products, the name ***Euthroid*** was considered to have the most potential for confusion with Unithroid, particularly with verbal prescriptions. However, Euthroid products were withdrawn from the U.S. market in 1993. A review of recent editions of standard references revealed either no listing or a notation that the product had been withdrawn. The last edition of PDR in which this drug product was listed is the 1993 edition. In the U.S., one brand of liotrix is marketed under the trade name ***Thyrolar*** (Forest). Prescriptions for Unithroid must specify a dose, which would differ from Euthroid combination product strengths.

TABLE 1

Product Name	**Dosage form(s), Generic name**	**Usual adult dose***	**Other****
Unithroid	Oral tablets: 0.025, 0.05, 0.075, 0.088, 0.1, 0.112, 0.125, 0.15, 0.175, 0.2, 0.3 mg (levothyroxine sodium [T_4])	12.5 to 300 mcg/day per pt response	
Euthroid-1	Oral tablets: 60 mcg T_4 & 15 mcg liothyronine (T_3) (liotrix). Withdrawn in 1993	Oral: One-fourth to two tablets per day (T_4 15 - 120 mcg), per patient response	S/A per OPDRA respondents
Euthroid-2	Oral tablets: 120 mcg T_4 & 30 mcg T_3 (liotrix) Withdrawn in 1993	See above.	S/A per OPDRA respondents;
Euthroid-3	Oral tablets: 180 mcg T_4 & 45 mcg T_3 (liotrix) Withdrawn in 1993	See above.	S/A per OPDRA respondents
Synthroid	Oral tablets: Same as Unithroid (levothyroxine sodium) Injection: 200 mcg, 500 mcg per vial	Oral: 12.5 - 200 mcg/day per pt response	S/A per OPDRA respondent
Unasyn	Injection: 1.5 and 3 grams per vial 1 g ampicillin/0.5 g sulbactam 2 g ampicillin/1 g sulbactam	IV: 1.5 to 3 grams every 6 to 24 hours.	S/A per OPDRA
Unidur	Oral: 400mg, 600mg extended release tablets (theophylline)	Oral: 400-1600 mg per day (adults) 10-36 mg/kg/day (1-9 y.o.)	L/A, S/A per OPDRA.
Uniphyl	Oral: 400mg, 600mg extended release tablets (theophylline)	Oral: 400-1600 mg per day (adults) 10-36 mg/kg/day (1-9 y.o.)	L/A, S/A per OPDRA
Unituss HC	Oral: combination antihistamine, antitussive, decongestant syrup	Oral: 5 – 10 mL every 4 - 6 hours, up to 40 mL per day.	L/A per OPDRA
Univasc	Oral: 7.5, 15 mg tablets (moexipril HCl)	Oral: 3.75 to 30 mg per day	L/A OPDRA
		*Frequently used, not all-inclusive.	**L/A (look-alike), S/A (sound-alike)

B. MEDLINE

MEDLINE was searched for published reports of medication errors occurring with levothyroxine, using the query terms "thyroxine", "thyroid", "synthroid", and "levoxine" along with the MeSH headings "Medical Errors" and "Medication Errors". ***Five citations*** *(2 cases plus comments) were retrieved using this strategy*. One (1) case was published in which **Lanoxin 0.125 mg** was dispensed erroneously for **Levoxine 0.125 mg**[vi,vii,viii,ix]. In another publication, a handwritten order for **levothyroxine 0.1 mg** was misinterpreted as **Lanoxin 0.1 mg**[x]. Because Lanoxin tablets are not available in a 0.1 mg strength, the pharmacist believed the physician ordered **Lanoxicaps,** which are available in a 0.1 mg capsule form.

C. AERS/DQRS/SRS DATABASE SEARCHES

Several levothyroxine sodium products have been marketed in the U.S. without an NDA. We searched the *FDA Adverse Event Reporting System (AERS)* database for all postmarketing safety reports of medication errors associated with levothyroxine products, using the Meddra Higher Level Terms MALADMINISTRATION AND ACCIDENTAL EXPOSURE and OVERDOSE and the suspect drug levothyroxine%. The *Drug Quality Reporting System (DQRS) and Spontaneous Reporting System (SRS)* databases were also searched for similar reports with levothyroxine%. The COSTART terms used to query the SRS database included OVERDOSE, OVERDOSE ACCID, and MED ERROR.

This search strategy retrieved an additional 16 medication error reports. The results of this search are summarized briefly in Table 2 (see Attachment 1, page 9). The two (2) published medication error reports are also included in these data.

In ten (10) cases, an incorrect drug was dispensed. Four (4) of these cases had a serious outcome, including one death. Most of these (n=6) were reports where Lanoxin and levothyroxine were confused with the other. The two drug names bear a strong visual resemblance to each other, especially with handwritten prescriptions, are prescribed for chronic use, have a similar dosing regimen (e.g., once daily), and have overlapping strengths (e.g., 0.125 mg). All of these qualities increase the potential for medication errors. In response, the manufacturer of Levoxine changed the product name to Levoxyl; three of our 6 cases involved Levoxine. Two (2) reports were received where Synthroid was confused with Premarin, both of which products are available in 0.3-mg tablets and given once daily as chronic medications. One (1) error occurred in which Synthroid 100 mcg was confused with Symmetrel 100 mg. The last report was an error in which a pharmacist filled a Synthroid-labeled prescription with a bottle of Risperdal that was being used to fill another patient's prescription at the same time.

In eight (8) cases, an incorrect dose of levothyroxine was dispensed. Three (3) of these cases had a serious outcome, including one death. Most of these (n=4) were reports where a decimal point error occurred and the patient received a 10-fold overdose. One (1) case was reported in which a pharmacist filled a Synthroid prescription with the incorrect strength (e.g. 150 mcg instead of 200 mcg). One (1) prescription for Synthroid "Q.D." was misinterpreted as "Q.I.D.". This is not an uncommon medication error associated with this abbreviation in handwritten prescriptions for other drugs as well. One (1) patient who had been taking Synthroid 25 *mcg* oral daily received a 25 *mg* intravenous dose of Synthroid prior to surgery; the outcome of this case was fatal.

In the remaining case, a two-fold overdose of the intravenous preparation of Synthroid occurred. The manufacturer's labeling states that the product, a lyophilized *powder* of 200 or 500 mcg, is supplied in a *10 mL vial*, which refers to the empty vial size. The wholesale supplier for that facility listed the product accordingly. The product is reconstituted, however, with *5 mL of diluent*, resulting in a final concentration of approximately 40 or 100 mcg per mL. Based upon the information provided by the wholesaler, the pharmacist calculated that 10 mL was the final volume, yielding an incorrect final concentration of 50 mcg per mL. The patient therefore received 1 mL (100 mcg) and not the correct dose of 0.5 mL (50 mcg). Errors caused by product labeling in this manner have been reported with other products as well. *As part of packaging and labeling reviews pertaining to safety, OPDRA recommends that empty vial sizes not be included and that the sponsors include the final concentration after dilution in the package insert.*

D. STUDY CONDUCTED BY OPDRA

1. Methodology

A study was conducted within FDA employing a total of 92 health care professionals (nurses, pharmacists, and physicians) to determine the degree of confusion of Unithroid with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Unithroid (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	**VERBAL PRESCRIPTIONS**
Outpatient: Unithroid 100 mcg, 1 po QD, #20, 1 refill	*Outpatient*: Unithroid 100 micrograms, take one everyday. Dispense 20 with one refill.
Inpatient: Continue Unithroid 100 mcg QD	

2. Results

Results of this exercise are summarized below:

Study	No. of participants	# of responses (%)	"Unithroid" response	Other response
Written: Outpatient	31	20 (65%)	17 (85%)	3 (15%)
Inpatient	31	20 (65%)	19 (95%)	1 (5%)
Verbal: Outpatient	30	14 (47%)	4 (29%)	10 (71%)
Total	92	54 (59%)	40 (74%)	14 (26%)

Among participants in the two (2) written prescription studies, 4 of 40 respondents (10%) interpreted the name incorrectly. The incorrect name interpretations generally were phonetic variations of Unithroid. *One participant interpreted the name as **Synthroid.***

Among verbal prescription study participants, 10 of 14 respondents (71%) interpreted the name incorrectly. Most of the incorrect name interpretations were phonetic variations of "Unithroid".

*However, **two** respondents interpreted the name as **Euthroid,** a brand of liotrix (thyroxine sodium plus liothyronine [T_3]) that is no longer marketed in the U.S. by Parke Davis.*

E. SAFETY EVALUATOR RISK ASSESSMENT

In the Expert Panel Discussion, there were no proprietary names of currently marketed U.S. products identified that were thought to have significant sound-alike, look-alike qualities with respect to Unithroid. Although a number of products contain "Uni" as the initial portion of the name, confusion of Unithroid with these products seems unlikely, given the differences in dosage forms, route of administration, usual dose, and dosing frequency.

We conducted prescription studies in an attempt to simulate the prescription ordering process. *In this case, two respondents to the verbal prescription studies interpreted the name as Euthroid.* However, Euthroid products were withdrawn from the U.S. market in 1993. A review of recent editions of standard references revealed either no listing or a notation that the product had been withdrawn. Prescriptions for Unithroid also would require specification of a dose, which would differ from Euthroid combination product strengths. Therefore, confusion between these two products seems unlikely. *One respondent in the written prescription studies interpreted the name as Synthroid,* a product that, if approved, will be considered generically equivalent to Unithroid.

For these reasons, we do not object to the use of the proprietary name "Unithroid".

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

A. Labeling and Packaging Issues

In the late stages of finalization of this review, the sponsor withdrew the name "Unithroid", proposed an alternate trade name [ ]", and provided a draft package insert and color copies of container labels for the product. Therefore, a complete labeling review for safety concerns will be conducted at the time of the OPDRA Proprietary Name Review for [ ]

Three issues have been identified in previous reviews of other levothyroxine products and in this review of the postmarketing medication error reports. *Inclusion of empty vial size* for levothyroxine lyophilized powder for injection has resulted in medication errors and should be deleted. *Final concentration of the product after dilution* should be provided in the package insert. OPDRA also recommends that *the container and tablet color for each strength of levothyroxine be consistent for all manufacturers* and *be the same as that of Synthroid*. This information will be reiterated in the OPDRA Proprietary Name Review for [ ].

B. Safety Related Issues

A number of medication errors concerning all levothyroxine products have been reported to FDA via the AERS database. Some of these errors had a serious outcome, including death.

1. **Errors continue to occur in which Levothyroxine is confused with Lanoxin** and vice versa. The potential for serious outcome is also great. Ideally, an educational campaign for health care practitioners would be helpful. We suggest the following messages, some of which are general principles of patient counseling to help prevent errors as well as to promote patient understanding of their medications and medical conditions.

a. **Prescribers** take *additional* time to *print* prescriptions for these two drugs. The two drug names bear a very strong resemblance in handwritten prescriptions. The *abbreviations "mcg" and "mg"* are also frequently confused with each other in handwritten prescriptions. *Provide both mg and the mcg conversion* for levothyroxine, such as "Levothyroxine 100 mcg (0.1 mg)" or "Synthroid 0.1 mg (100 mcg)". Prescriptions for Lanoxin are rarely written as "Lanoxin 125 mcg or 250 mcg". This will also provide a *check for decimal point errors* that can occur in mentally converting the dose from mcg to mg or vice versa. *Write the use* of these 2 drugs on their respective prescriptions in a short notation such as "Heart" or "Thyroid". Make *certain the patient understands* this and *verifies* this with the pharmacy when the prescription is filled.

b. **Pharmacists** take *additional* time when dispensing Lanoxin or levothyroxine. *Ask the patient* if they know for what condition the drug has been prescribed. If the patient is not certain or cannot reliably provide the information, *call the physician* to verify the order. *Consider storing one of the two products* in a separate part of the pharmacy. This will provide a break from the usual pattern of choosing the drug product needed to fill the prescription. *Carefully restock unit-dose bins* of either drug with returned doses of Lanoxin or levothyroxine. *Note on the prescription label* what the drug is used for ("Heart", "Thyroid") and verify this with the patient when the prescription is dispensed.

c. **Patients** ask your doctor *what the prescription is written* for. If the *prescription seems unreadable* to you, ask for a new one. Ask your pharmacist if you have *any doubt about the appearance of the tablets. Tell the pharmacist any information* that you know about your prescriptions when you take them to the pharmacy and before they are filled. Information such as "This is for my heart (or thyroid) condition" is very helpful. Ask for a *pharmacist to explain the medication* to you when you pick it up. If the pharmacy seems too busy, *ask if there is a less busy time or pharmacy* to have your prescriptions filled.

2. Errors continue to occur in which a decimal point is misplaced or in converting from microgram to milligram doses

a. **Prescribers** always *write a leading zero* for doses of less than 1 mg. Prescriptions written in a format such as "Synthroid .025 mg" often are misread as "Synthroid 0.25 mg" and result in a 10-fold overdose. *Never include trailing zeros* such as "Synthroid 25.0 mcg", as this format is often misread as "Synthroid 250 mcg". The *abbreviations "mcg" and "mg"* are frequently confused with each other in handwritten prescriptions. *Provide both mg and the mcg conversion* for levothyroxine, such as "Levothyroxine 100 mcg (0.1 mg)" or "Synthroid 0.1 mg (100 mcg)".

b. **Pharmacists** check the patient's records *for previous prescriptions*. If the dose appears to have changed, ask the patient or physician if that is intentional. *Recheck any calculations* done to convert dosing from mg to mcg or vice versa.

c. **Patients** ask your doctor *if your prescription has changed* in any way from a previous prescription. Ask your pharmacist if you have *any doubt about the appearance of the tablets*, such as color, or if a *different dose* than what you expected appears on the label. *Tell the pharmacist any information* that you know about your prescriptions when you take them to the pharmacy and before they are filled. Information such as "My doctor changed the dose of my medication to a lower strength today" is very helpful.

IV. RECOMMENDATIONS

A. From a safety perspective, OPDRA does not object to the use of the proprietary name "Unithroid".

B. A number of medication errors have been reported and still occur with the use of levothyroxine. We have provided suggestions for prevention of additional medication errors.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3245.

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Carol Pamer, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

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Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

ATTACHMENT 1
TABLE 2 Postmarketing Safety Reports of Medication Errors Associated with levothyroxine

Intended product	Dispensed product	Outcome	Cause(s)	AERS #
Incorrect Dose (n=8)				
Synthroid 50 mcg QD	Synthroid 50 mcg QID	Hospitalized	Misinterpretation	M1759043
Levothyroxine 0.25 mg	Levothyroxine 0.025 mg	Hospitalization prolonged	Dispensing error	3447501-0-00-01 3298068-1-00-01
Synthroid 0.05 mg	Synthroid 0.5 mg	N/A	Transcribing error	3276603-7-00-01
Synthroid 50 mcg IV	Synthroid 100 mcg IV	Unknown	Confusing labeling	3160500-1-00-02
Synthroid 25 mcg (oral)	Synthroid 25 mg IV	Death	Unknown	M1928470
Synthroid unknown dose	Synthroid 10-fold OD	Death	Decimal point error	3131101-6-00-01
Levothyroxine 200 mcg	Levothyroxine 150 mcg	Nonserious	Wrong strength chosen	3501404-1-00-01
Levothyroxine 25 mcg	Levothyroxine 0.25 mg	Hospitalized	Unknown	M598228
Incorrect Drug (n=10)				
Levotab 0.125 mg ii QD	Lanoxin 0.125 mg ii QD	Nonserious	Dispensing error	3271031-2-00-01
Levothyroxine 0.1 mg	Digoxin 0.25 mg	ER evaluation	Dispensing error	3179691-1-00-01
Levoxine 0.1 mg	Lanoxicaps 0.1 mg	Unknown	Rx Handwriting	Cohen MR, 1993
Lanoxin 0.125 mg	Levoxine 0.125 mg	Nonserious	Dispensing error	3135405-2-00-01
Levoxine 0.125 mg daily	Lanoxin 0.125 mg daily	Unrelated death	Rx Handwriting	Pourmotabbed G, 1995
Synthroid 0.125 mg	Digoxin 0.125 mg	N/A	Dispensing error	3495414-0-00-01
Synthroid	Premarin	Disability	Dispensing error	3135646-4-00-01
Premarin	Synthroid 0.3 mg QD	Hospitalized	Dispensing error	3073261-1-00
Symmetrel 100 mg	Synthroid 100 mcg	N/A	Order entry error	3327499-6-00-01
Synthroid 0.15 mg	Risperdal 2 mg	N/A	Dispensing error	3392865-X-00-01

[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

[ii] American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

[iii] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

[iv] COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

[v] WWW location http://www.uspto.gov/tmdb/index.html.

[vi] Pourmotabbed G. The naming of drugs is a difficult matter (letter) [see comments]. NEJM 1994 Oct 27; 331(17):1163.

[vii] Levinson ML, Saine DR. More on drug-name confusion (letter, comment). NEJM 1995 Mar 16; 332(11):755.

[viii] Franklin K. More on drug-name confusion (letter, comment). NEJM 1995 Mar 16; 332(11):755.

[ix] Kramer JM. More on drug-name confusion (letter, comment). NEJM 1995 Mar 16; 332(11):754-5.

[x] Cohen MR. Levoxine order could be misread. Nursing 1993 Jan; 23(1):25.